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Monozygotic twins discordant for sex*

Summary. A pair of monozygotic, adolescent twins is discordant for sex. The phenotypic female twin has a chromosome constitution of 46,XY/45,X. She displays many signs of Turner's syndrome, including typical facies, webbed neck, malformed left kidney, high plasma gonadotropins, and streak ovaries. However, her height is 154 cm which exceeds the height usually reported in Turner's syndrome. The male twin has a karyotype of 46,XY and normal sexual development. Only two other reports of pairs of monozygotic twins of opposite sex have been published.

In 1961 Turpin *et al* reported a pair of monozygotic twins of apparent opposite sex. The boy, who was normal in his physical appearance, had a normal 46,XY chromosome complement, while the girl had the typical features of Turner's syndrome, with a chromosome constitution of 45,X. Another twin pair, discordant for sex, has been described by Edwards, Dent, and Kahn (1966). However, the cytogenetic studies revealed different karyotypes, namely 45X/46XY in the female, who had signs of Turner's syndrome, and 45,X in the phenotypically normal male. The authors assumed that both twins had a chromosome complement of 46,XY/45X, though the 46,XY line could not be demonstrated in the male. A third pair of monozygotic twins, with somewhat similar features, but not discordant for sex phenotypes, was described by Russell *et al* (1966). Despite the presence of some degree of virilization, which was more prevalent in one member of the pair, the female sex was assigned to both twins. Twin I had bilateral streak ovaries and a karyotype of 45,X, while twin II had ambiguous genitalia, a streak ovary on one side, and an immature testis on the contralateral side. Her karyotype showed 45,X/46,XY mosaicism.

We wish to describe an additional pair of monozygotic twins, discordant for sex, in which the girl shows features of Turner's syndrome and a 46,XY/45,X karyotype, whereas her twin is a normal boy with a 46,XY chromosome constitution.

Case report

The twins were born in August 1957 after an uneventful 36 weeks' pregnancy. The mother was 25 years and the father 27 years old at the time of the delivery. Both parents are living and well. The twins are the product of their mother's first and only pregnancy. Twin I was a girl who presented at birth with the typical features of the Bonnevie-Ullrich syndrome. She had a webbed neck and swelling of the feet and hands. Her birthweight was 2410 g. Twin II was a normal boy, his birthweight was 2640 g. His subsequent development has been normal.

D.F., twin I, was seen first at the Albert Einstein College of Medicine at the age of 14 years 5 months, because of short stature and absence of normal adolescent development. She is an intelligent girl whose height at that age was 143.7 cm (below the 3rd centile). Her weight was 40 kg (3rd centile). Blood pressure was 112/76 and 110/80 mmHg. She had epicanthic folds, notched pinnae, and signs of a webbed neck which had been operated on at the age of 13 years. The hair line was very low, with hair extending to the top of the right shoulder. The palate was high and narrow. The carrying angle of the arms was increased. There was no breast development and the nipples were widely spaced. Pubic hair was sparse. The external genitalia were female in appearance, without any signs of ambiguity. At the age of 15 years her height was 154 cm (10th centile), weight 42.6 kg (5th centile). At this age cyclic treatment with oestrogens was initiated. Subsequently vaginal bleeding occurred on schedule, but breast development has been minimal.

Investigation and results

Routine blood and urine tests were within normal limits.

Hormonal studies revealed normal thyroid tests—

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T_4-5.1, T_3 uptake 33%, T_4 displacement—8.3, FT_4-9%. Gonadotropins were raised, FSH-74 mU/l and LH more than 100 mU/l.

X-rays of the hands and wrists showed normal configuration of the bones, with a bone age of 13 years (at a chronological age of 15 years, 8 months). The pelvis had an android configuration. An intravenous pyelogram revealed malrotation of the left kidney.

Laparotomy and gonadal histology. At age 15 years 8 months, a laparotomy was performed. A small uterus with Fallopian tubes and bilateral streak ovaries were found. The ovaries were removed. Microscopical examination of the left gonad revealed a streak ovary with only connective tissue and some structures that resembled fimbria. The right streak gonad contained clear round cells which were defined as hilar cells. No evidence of testicular tissue was found.

Cytogenetic studies (Table I). Buccal smears were repeatedly negative for X bodies and positive for Y bodies. Lymphocyte cultures on 3 different occasions revealed a chromosome complement of 46,XY. Fibroblast cultures, derived from a skin biopsy of the upper arm revealed a karyotype of 45,X. Cultures from the right gonad had a 45,X chromosome constitution. Cultures from the left gonad were unsuccessful. Lymphocyte cultures of the brother and parents revealed normal karyotypes. Differential banding with mepacrine (Caspersson, Lomakka, and Zech, 1971) showed identical chromosomes in both twins, and the Y chromosomes of both twins resembled their father's Y.

Dermatoglyphs. Table 2 and the Figure summarize the findings in the twins. As would be expected for monozygotic twins, the course of the main lines on the palms is similar. However, there are differences in patterns on the fingertips involving the thumbs, left index finger, and right ring finger. The maximal *atd* angle is similar. The total ridge count as well as the *a-b* ridge counts are higher in twin I than in her brother. These differences can be explained by the differences in the chromosome

TABLE I

CYTOGENETIC FINDINGS ON THE TWINS AND THEIR PARENTS

Subject	Buccal Mucosa Sex Chromatin Pattern	Tissue	Number of Cells Studied	Karyotype
D.F. twin I	Positive Y body Negative X body	Blood	60*	46,XY
		Skin	30	45,X
		Gonad/rt	13	45.X
R.F. twin II	Positive Y body Negative X body	Blood	60*	46,XY
Mother	Positive X body Negative Y body	Blood	20	46,XX
Father	Positive Y body	Blood	20	46,XY

* Summary of 3 separate cultures.

TABLE II

DERMATOGLYPHIC FINDINGS ON THE TWINS

	Digital Patterns and Ridge Counts										Total Ridge Count
I. *Finger Tips*	*Left*					*Right*					
D.F. Twin I	V UL 17	IV UL 18	III UL 16	II UL 19	I UL 22	I UL 23	II RL 18	III UL 19	IV UL 19	V UL 16	187
R.F. Twin II	UL 9	UL 13	UL 14	RL 14	W 17/11	W 19/15	RL 8	UL 11	CpUL 17	UL 9	131

II. *Palms*	*Left*	*Right*	*Total*
II. *Palms*			
a) *a-b ridge count*			
D.F. Twin I	55	56	111
R.F. Twin II	47	48	95
b) *Maximal atd angle*			
D.F. Twin I	46	48	94
R.F. Twin II	45	48	93

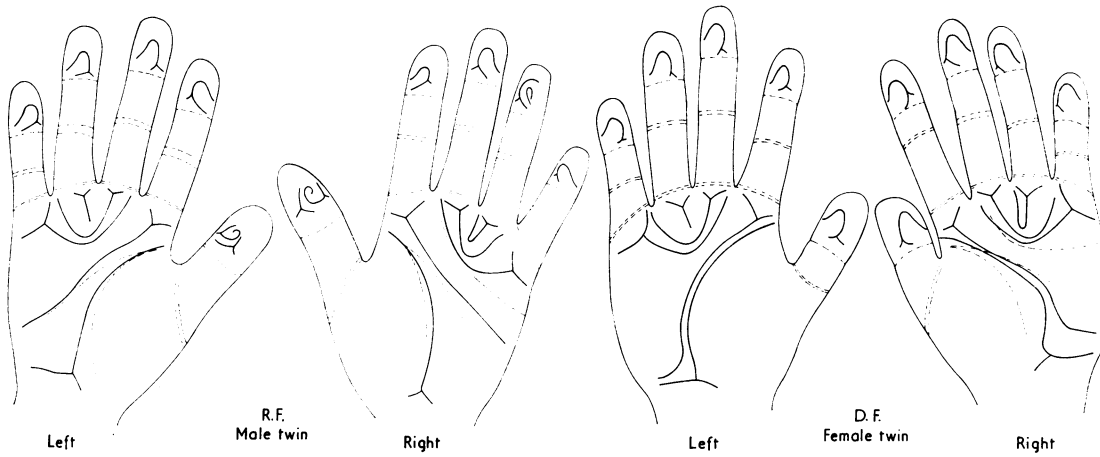

FIG. Hand prints of the twins, D.F. and R.F.

constitution. Females with a 45, X sex chromosome complement are known to have a significantly higher total ridge count as well as *a-b* ridge count (Holt, 1968).

Zygosity studies. A number of blood group antigens and serum proteins and enzymes were investigated (Tables III and IV). The twins are identical for all tests. They could have differed in the Rh, P, MN, Duffy, Xg^a, GM, haptoglobin, and acid phosphatase phenotypes.

TABLE IV

SERUM PROTEIN AND ENZYME PHENOTYPES OF THE TWINS AND THEIR PARENTS

Subject	Gm			Hp	Gc	Oro	AcPh
	a	b	x				
D.F., Twin I	+	+	+	1–2	2–1	FS	AB
R.F., Twin II	+	+	+	1–2	2–1	FS	AB
Mother	+	−	+	1–2	1	FS	AB
Father	−	+	−	2	2	FS	B

All are Inv-neg., Tf C, Ag(x−y+), PGM_1 1, C3 S, Hgb A, ADA 1, Esterase-D 1, GPT 1, AK A, PCE nl, Bf S, oroso mucoid F.

Discussion

Because the twins have identical phenotypes for all markers shown in Tables III and IV, they are probably monozygotic twins. The probability that they would have been identical if they were dizygous is $0.0026 - 0.5(RH) \times 0.5(Fy) \times 0.25(P), \times 0.25(MN) \times 0.89(Xg^a) \times 0.75(Gm) \times 0.5(Hp) \times 0.5$(acid phosphatase). Allowance was made for the probability that the mother is heterozygous for $Xg^a(0.53)$ and for $Gm^{ax}(0.80)$.* Calculations were based on the probability that the phenotypes of the second child would have duplicated those of the first child by chance alone. For the purpose of the calculations, the children were assumed to be dizygous.

The dermatoglyphs are similar in many respects

* Gene frequencies in caucasians are 0.64 for Xg^a, 0.36 for Xg, 0.12 for Gm^{ax}, and 0.24 for Gm^a.

TABLE III

ERYTHROCYTE GROUPS OF THE TWINS AND THEIR PARENTS

Subject	ABO	Rh	Kell	Duffy		Kidd		P_1	MN	Xg^a
				Fy^a	Fy^b	Jk^a	Jk^b			
D.F., Twin I	O	Rh_1Rh_1	kKp^b	+	+	+	+	−	Ns	+
R.F., Twin II	O	Rh_1Rh_1	kKp^b	+	+	+	+	−	Ns	+
Mother	O	Rh_1rh	kKp^b	+	+	+	−	+	MNs	+
Father	O	Rh_1Rh_1	kKp^b	−	+	−	+	+	MNs	+

All are Lu(a−).

(Fig.). However, the ridge counts are much higher in twin I than in twin II (Table II). It is well known that females with Turner's syndrome have higher counts than normal males. A similar difference in ridge counts has been observed by other authors in monozygotic twins, discordant for Turner's syndrome (Edwards *et al*, 1966; Potter and Taitz, 1972).

While there are at least 22 pairs of monozygotic twins with Turner's syndrome and a 45,X chromosome pattern (Riekhof *et al*, 1972) and at least eight pairs of female monozygotic twins, discordant for Turner's syndrome (Shine and Corney, 1966; Potter and Taitz, 1972), only two pairs of monozygotic twins, discordant for sex, have been described previously (Turpin *et al*, 1961; Edwards *et al*, 1966). A third pair of twins had ambiguous external genitalia, but were assigned the female sex. One of them showed a cell line with 46,XY karyotype in addition to cells with a 45,X chromosome constitution (Russell *et al*, 1966). Thus, twinning in an XY zygote and subsequent mitotic error, seems to occur much less frequently than in the XX zygote.

Since both twins described in this report have a Y chromosome, it is likely that they originated from a 46,XY zygote. Subsequently twin I, through mitotic error, lost the Y chromosome in the majority of tissues, though it has been retained in the blood forming tissues. This process must have occurred very early in embryonal life, even before the formation of the primordial gonadal cells, leading to the formation of streak gonads, without evidence of testicular tissue or ambiguous genitalia. Evidence for this early origin is supported by the differences in dermatoglyphic patterns which in twin I is typical for Turner's syndrome (Penrose and Ohara, 1973).

Twin I displays many signs of Turner's syndrome —typical facies, high arched palate, webbed neck, low hair line, shield chest with widely spaced nipples, cubitus valgus, kidney abnormalities, and streak gonads. Though she is quite short, her height of 154 cm is greater than the average height described in Turner's syndrome (Engel and Forbes, 1965). However, this finding has been reported in individuals with the so-called 'mixed gonadal dysgenesis' syndrome (Davidoff and Federman, 1973). These individuals, who are mosaic for 45,X and 46,XY chromosome cell lines and usually display some degree of virilization, in addition to some signs of Turner's syndrome, exceed the reported height of patients with the classical Turner's syndrome. Thus, the greater height in twin I might reflect the presence of the Y chromosome. A characteristic finding in mixed gonadal dysgenesis is the presence of a unilateral streak gonad and a primitive testis on the contralateral side. In our patient, however, streak gonads were present bilaterally and thorough microscopy failed to reveal any evidence of testicular tissue. This finding is unusual and might reflect the presence of a majority of 45,X cells in this girl. Only 45,X cells were found in cultures from the right gonad and in skin fibroblasts. Unfortunately cell cultures from the left gonad were unsuccessful and skin biopsies were not obtained from both sides of her body. However, repeated buccal smears did reveal the presence of a fluorescent Y chromatin mass and all lymphocyte cultures showed a 46,XY chromosomal constitution.

Twin II is a normal healthy male who exceeds 6 feet (180 cm) in height and shows normal male sexual development. He has no evidence of chromosomal mosaicism in blood cultures. However, since other tissues have not been studied, mosaicism cannot absolutely be ruled out.

Russell *et al* (1966) in their discussion of their paper suggested four possibilities of mitotic error in a pair of twins derived from a zygotic nucleus with an XY sex chromosome composition. Type 1—X and XY, type 2—X/XY and XY, type 3—X and X/XY, and type 4—X/XY and X/XY. Type 1, 3, and 4 have been described previously. Our pair of twins appears to represent type 2 which has not been described hitherto.

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Addendum

Since this paper was submitted for publication, another pair of monozygotic twins, discordant for phenotypic sex, was described (Karp *et al*, 1975). As in our case, the normal male had a karyotype of 46,XY, while the female's chromosome constitution was 46XY/45X, similar to our case. However, the phenotypic female twin had an enlarged clitoris and histology of one gonad showed some testicular structures. This girl also had fewer clinical signs of Turner's syndrome than our patient. Thus the case of Karp *et al* could have been assigned to the syndrome of mixed gonadal dysgenesis (Davidoff and Federman, 1973).

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An XX female with sexual infantilism, absent gonads, and lack of Müllerian ducts*

Summary. A patient with a 46,XX chromosome constitution showed the following main characteristics: lack of secondary sexual development, female external genitalia with absence of vagina, no gonadal structures, and complete lack of internal genitalia. This is a variant of the gonadal agenesis syndrome so far only described in association with an XY chromosome component. Endocrinology demonstrated that in the absence of gonadal feedback the pituitary responsiveness to synthetic luteinizing hormone-releasing hormone was increased.

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Reports of agonadism are scarce (Overzier and Linden, 1956; Philipp, 1956; Chaptal *et al*, 1958; Dewhurst *et al*, 1963; Emson and Buckwold, 1965; Sarto and Opitz, 1973; Levinson *et al*, 1975) and its aetiology remains ill understood at this time. Hitherto, all patients with gonadal agenesis syndrome have been found to possess an XY karyotype so that it has been suggested that the fetal testis was functional for a sufficient time to induce the Müllerian duct inhibition, but not long enough to maintain Wolffian duct development. A short activity of the fetal testis would also account for the partially virilized external genitalia which is a common finding in these patients. The syndrome has been discussed under various names as 'true agonadism', 'vanishing testicles', 'XY female with absent gonads', and 'the XY gonadal agenesis syndrome'. The purpose of the present communication is to report what is, to our knowledge, the first case of gonadal agenesis associated with a 46,XX sex chromosome constitution.

Case report

The proband, aged 17, was admitted to hospital on 9 August 1974, because of primary amenorrhoea and retardation of sexual development. The patient had been brought up as a woman since she had a feminine phenotype (Fig. 1). Height was 145 cm, lower segment 75 cm, span 147 cm; weight was 45 kg. Breasts were prepubertal and axillary hair was absent. External genitalia (Fig. 2) showed immature labia majora and

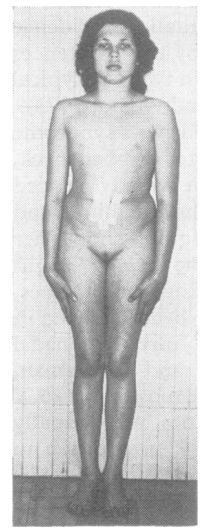

FIG. 1.

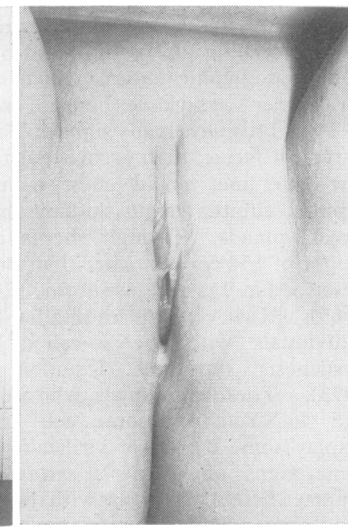

FIG. 2.

FIG. 1. General appearance of the patient.
FIG. 2. The external genitalia show the normal infantile type.